



The Honorable Elijah E. Cummings
Ranking Member
Committee on Oversight and Government Reform
House of Representatives
Washington, D.C. 20515-6143

JUL 23 2012

Dear Mr. Cummings:

Thank you for your letter of July 9, 2012, regarding the report entitled “FDA’s Contribution to the Drug Shortage Crisis” (the Report).¹ We appreciate the opportunity to provide clarification about the issues raised in the Report.

Preventing drug shortages is a top priority for the Food and Drug Administration (FDA or the Agency). The number of drug shortages has risen steadily since 2005 to hit an all-time high of 251 drug shortages in 2011. This is a very troubling situation that FDA takes very seriously. The root causes of drug shortages, however, lie largely outside of FDA’s purview. Contrary to the conclusion reached in the Report, FDA is not the root cause of this serious public health problem. In recent years, more than half of all drug shortages were related to manufacturing production problems, including quality-related issues and delays. The remainder of the shortages was caused by business decisions to discontinue certain products, difficulty obtaining raw materials, loss of manufacturing sites, increased demand, and component problems.²

Patients expect and deserve high-quality drugs. It is the manufacturer’s responsibility to ensure that its products are safe, effective, and of high quality. FDA is committed to working with industry to resolve quality or manufacturing problems that arise, to ensure continued patient access to vital safe and effective medicines. In fact, in appropriate cases, FDA may exercise regulatory flexibility to prevent or mitigate a drug shortage, such as by expediting inspections or review of manufacturing supplements to facilitate production changes.

When products manufactured under problematic manufacturing conditions pose a safety threat to patients—such as glass shards or metal shavings in vials of injectable drug products or fungal contamination of the product—manufacturers generally must stop production to resolve the problem before resuming manufacturing and distribution. Although FDA can work closely with

¹ <http://oversight.house.gov/wp-content/uploads/2012/06/6-15-2012-Report-FDAs-Contribution-to-the-Drug-Shortage-Crisis.pdf>

² U.S. Department of Health and Human Services, U.S. Food and Drug Administration. “A Review of FDA’s Approach to Medical Product Shortages.” October 31, 2011. Available at <http://www.fda.gov/downloads/AboutFDA/ReportsManualsForms/Reports/UCM277755.pdf>

manufacturers to help resolve the problems and get back online, FDA alone cannot solve the drug shortages crisis. The long-term solution to this problem requires a significant commitment on the part of drug manufacturers to invest in their infrastructure and to keep FDA informed about potential manufacturing and quality problems that potentially could lead to shortage situations. Drug shortages legislation enacted as part of the Food and Drug Administration Safety and Innovation Act (FDASIA) (P.L. 112-144) will provide the Agency with important new tools to help ensure that patients have access to the lifesaving medicines they need.

The new legislation expands the scope of mandatory reporting by manufacturers of situations that may lead to drug shortages, including both permanent discontinuances and short-term disruptions in supply. The legislation requires manufacturers to report potential shortage situations to FDA at least six months in advance, or where that is not possible, as soon as the manufacturer learns of the issue. Early notification by manufacturers of potential drug shortages is critical to our ability to prevent shortages or mitigate the effect of unavoidable shortages on patients who need these drugs.

FDA responds to potential drug shortages by taking actions to address their underlying causes and enhance product availability. FDA determines how best to address each shortage situation based on its cause and the public health risk associated with the shortage. In 2011, FDA was able to help prevent 195 drug shortages. To date in 2012, we have been able to avert more than 90 shortages, and we were greatly assisted by early notification from manufacturers following the President's Executive Order in October of last year. We use a variety of tools to respond to drug shortage notifications, the most important of which include:

- Working closely with manufacturers to help them resolve the manufacturing and quality issues that are contributing to the short supply;
- Expediting FDA review of submissions from manufacturers that could alleviate the shortage;
- Identifying additional manufacturers who have the capacity and willingness to initiate or increase production of the drug in shortage;
- Helping firms to qualify new sources of raw material, when faced with a raw material shortage;
- Working with manufacturers to implement short-term, work-around solutions, when the risk to patients of the work-around solution is acceptable when weighed against the risk of not receiving the drug (for example, by allowing a product with particulate matter to be distributed with the use of a filter to eliminate the particulates); and
- Using enforcement discretion for temporary import of a non-U.S. product, after ensuring there are no undue safety or efficacy risks for U.S. patients with the non-U.S. product and ensuring it is manufactured in a facility that meets FDA quality standards.

FDA's efforts to date demonstrate that FDA is an important part of the solution to the drug shortages problem. By working closely with manufacturers experiencing problems, as well as potential alternative manufacturers, and by exercising regulatory flexibility to help mitigate shortages, FDA has had a substantial positive impact on the shortage situation. In addition, FDA's response to the increasing trend of drug shortages underscores the importance of strong

collaboration and constant communication among FDA, industry, health professionals, and patients.

We have restated your questions below in bold, followed by FDA's responses.

- 1. The report references warning letters sent to several companies that manufacture drugs that are or have been in short supply, suggesting that FDA actions inappropriately resulted in the shutdown of these facilities. Please explain why FDA believed it was necessary to send warning letters or take other action against these companies. Please provide a brief history of the activities at these facilities resulting in FDA's enforcement actions, and please provide a summary of 483-inspection findings and how underlying manufacturing concerns related to product safety.**

A key part of FDA's mission is ensuring that drug products on the U.S. market meet appropriate quality standards. Warning Letters may be issued when manufacturers fail to meet those standards, detailing the violations and the steps the manufacturer must take to come into compliance. Before issuing a Warning Letter, the Office of Compliance in the Center for Drug Evaluation and Research (CDER) consults with CDER's Drug Shortage Program staff to discuss the potential consequences of issuing the Warning Letter. Together, and with input from other parts of the Agency as necessary, these offices balance the risks of a potential drug shortage against the risk posed by the quality issues the manufacturer is experiencing. Regardless of whether the Agency decides to issue a Warning Letter, FDA works proactively with firms experiencing manufacturing quality issues to minimize the impact on the U.S. drug supply and to avert shortages.

With regard to the facilities referenced in the Committee's report, the majority of the Warning Letters or other regulatory actions were related to deficiencies in manufacturing processes and product quality that posed a safety risk to patients. These risks included endotoxin contamination, which may cause severe fever and death; the presence of metal particles in sterile drugs, which can cause serious injury to patients when injected; and overfill of vials of liquid morphine, which could result in caregivers administering an accidental overdose to patients. In these instances, FDA determined that the failure to adhere to appropriate standards, leading to product quality problems, warranted issuing a Warning Letter or taking other regulatory action.

To be clear, in the case of the manufacturers referenced in the report, it was the manufacturers who made the determination to stop producing drugs. FDA did not require the firms to shut down and even worked with each of them to try to avoid a shutdown, offering assistance to help assess and address manufacturing and quality concerns. Such assistance involved regular communication with the firm to discuss remediation and progress and helping firms prioritize remediation of systems and problems that pose the highest risk to patients. After the shutdown, FDA tried to avoid shortages by utilizing other tools, such as asking other manufacturers to initiate or increase product, accelerating review of applications, or exercising enforcement discretion for the temporary import of products from abroad.

Below, we briefly discuss some of the serious manufacturing or quality problems found at the four firms cited in the report that led to Form 483s and/or Warning Letters. (For more detailed

information, please refer to the enclosure, FDA Form 483s and Warning Letters Related to Four Major Pharmaceutical Manufacturers.)

Teva: Multiple reports of serious injury and illness related to the use of Teva's Propofol Injectable Emulsion product prompted an inspection of the facility in July 2009. The inspection confirmed the presence of endotoxins in finished product, which are parts of bacteria cells that if injected into the body cause a severe fever and even death. Multiple lots of product were recalled. FDA issued a Warning Letter to Teva on December 11, 2009, citing significant violations affecting the manufacture and quality of propofol and several other drugs. These violations included: failure to test ingredients and final products for endotoxins; inability to determine the cause of an out-of-trend level of bacterial endotoxin contamination found in three vials of Propofol Injectable Emulsion; and failure of the equipment used to clean and sterilize the glass vials used to hold sterile injectables, along with a failure to evaluate the impact of this equipment failure on lots produced before the failure was discovered. Teva voluntarily shut down its Irvine, California facility on April 16, 2010, to address these problems. They re-opened their facility on April 24, 2012, but have not resumed the manufacturing of propofol.

Ben Venue Labs (BVL)/Bedford Labs: BVL conducted 10 voluntary product recalls between January and November 2011 for reasons including lack of sterility assurance, glass and stainless steel particles, and low-fill volume in sterile injectable drugs, including cancer drugs. In May 2011, FDA conducted an inspection of BVL's Bedford, Ohio facility, during which 48 current Good Manufacturing Practice (CGMP) violations were discovered. These violations included: aseptic facility design that did not maintain a sterile environment; failure to investigate or take corrective action against microbial contamination; tools and materials used in aseptic fill rooms that appeared to be covered in rust; inadequate procedure for handling non-viable particulate incursion; and lack of retraining of staff, who were found to be using improper aseptic practices and equipment. In response to these findings, FDA issued a Form 483 to BVL. In November 2011, BVL voluntarily instituted a shutdown of its manufacturing facility to address problems including: roof leakage, flooding, and increasing amounts of mold in the manufacturing area; air filtering system failures in the sterile manufacturing area, resulting in unfiltered air in the clean room; and reports of visible metal particles in sterile injectable cancer drugs.

Hospira: Hospira's multiple manufacturing locations experienced substantial problems, including: stainless steel particle contamination affecting several injectables, including propofol; leakage of sterile units, which could lead to contamination and incorrect dosing; and overfilling of drug cartridges, including morphine, by as much as twice the indicated amount, a defect that could lead to incorrect dosing, respiratory distress, and in severe cases, death. Hospira conducted a voluntary recall of particulate contaminated products in 2009 and 2010, leading to shortages of affected products. FDA issued a Warning Letter to Hospira on April 12, 2010, after identifying significant violations of cGMP regulations during a January – February 2010 inspection of two of their facilities in North Carolina. FDA also issued Form 483s to Hospira in April, May, and July of 2011, addressing problems observed at their Texas and North Carolina facilities.

Sandoz/Novartis: Sandoz, owned by Novartis, has a site in Canada that makes sterile injectable products for the U.S. market. FDA inspection of that site led to the issuance of a Warning Letter in November 2011, citing concerns with unusual crystal formation in some batches of sterile drug products distributed to the United States. Crystals in injectable solutions could lead to patient injury requiring medical intervention, or a disruption in the concentration of the drug, making it less effective. Sandoz voluntarily suspended some production of these products to correct the quality concern. In December 2011, Novartis announced a voluntary shutdown to address widespread quality defects and manufacturing failures, identified after more than 1,360 complaints of foreign, stray, and broken tablets found in opiate products. FDA issued Form 483s to Novartis in July 2011 and January 2012, after inspections of Novartis' Nebraska facility revealed a failure to investigate consumer complaints in an adequate fashion. FDA also issued a Public Health Advisory to alert health care professionals and patients of the possible contamination of the opiate products manufactured by Novartis. The manufacturing issues Sandoz and Novartis experienced also compromised the sterility of the products and could result in contaminated products that would severely injure patients if administered.

- 2. The report asserts that a majority of shortages have been caused by excessive regulation and enforcement actions related to manufacturing issues. In contrast, FDA reported in October 2011 that 43% of shortages were caused by problems at manufacturing facilities, and that the remaining 57% of shortages were caused by a variety of other problems, many of which fall outside of the scope of the agency's purview, including delays in manufacturing or shipping (15%), shortages of ingredients (14%), and manufacturers' business decisions to discontinue production (8%). Please provide updated data regarding the causes of drug shortages reported through May 2012.**

- 6. To provide a more complete public record on this matter, please provide a brief description on the primary causes FDA believes are behind both current and recent increases in drug shortages.**

As we discuss in more detail in our response to Questions 4 and 5 below, there have been no recent changes in cGMP standards, and no evidence of excessive enforcement actions related to manufacturing issues that could cause drug shortages. FDA uses flexible and creative strategies to address drug shortages, but manufacturers are ultimately responsible for producing high quality, safe, and effective products. Their commitment to quality includes the responsibility to properly maintain their manufacturing facilities to avoid having to shut down the facilities because of severe manufacturing and quality problems.

As for recent information about the sources of drug shortages, during 2011 nearly 70 percent of all drug shortages were related to manufacturing production problems, including quality-related issues and delays. The remainder of the shortages were caused by business decisions to discontinue certain products, difficulty obtaining raw materials, loss of manufacturing sites, increased demand, and component problems. So far, in 2012, quality-related problems and delays have continued to account for the majority of shortages, especially those involving sterile injectable drugs.

- 3. The report states that it “could not find any evidence that any of the products produced at the facilities undergoing remediation had harmed anyone.” It is our understanding that manufacturers are required to submit Field Alert Reports (FARs) within three days of becoming aware of quality-related problems with their approved drug products. In addition, FDA may receive reports of product quality problems and adverse events from the public through its MedWatch web site. Please describe the number and content of FARs and Medwatch reports regarding the products listed in the report, as well as a description of FDA actions to respond to these FARs and Medwatch reports.**

FARS and MedWatch reports can provide information the Agency uses to identify quality problems, but they are often not the best indicator. The data captured in these systems is used to identify signals for follow up, and in the cases described in the response to Question 1 above, inspections disclosed substantial product quality and manufacturing deficiencies that pose serious risk to patients. Those problems were discussed in the inspection reports.

With respect to actual adverse events, FDA data indicate that there have been serious adverse events associated with contaminated products being administered to patients, and reports of product recalls to address serious concerns such as metal particles in sterile injectable drugs. For example, in July 2009, there were a total of 41 reported patients with post-operative chills and flu-like symptoms associated with Teva’s propofol containing elevated levels of endotoxins. Teva recalled several lots of this product and shut down to correct quality problems at its facility, affecting the production of propofol and several other drugs.

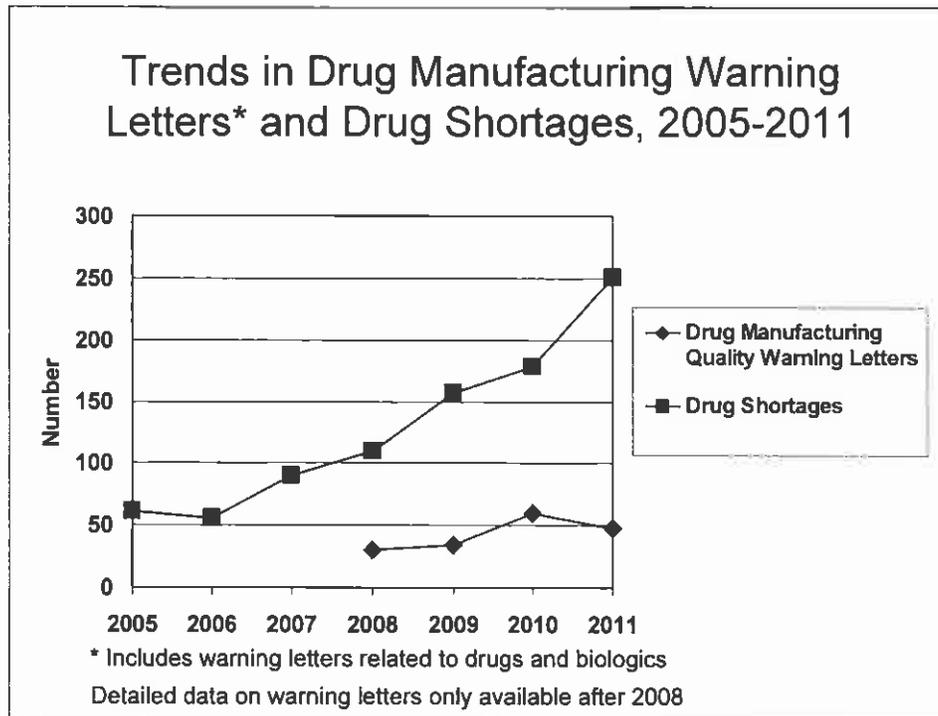
In addition, there were several Class 1 recalls of drug products at the facilities described in the report before they shut down. A Class 1 recall, by definition, indicates a potential serious risk to public health. FDA typically receives a FAR report in connection with a product recall. FDA obtained further information about serious problems at the affected facilities through follow-up inspections and communications with the affected firms, as noted above.

- 4. The report includes on page 17 a figure entitled “FDA Warning Letters, Fiscal Years 2004-2011” displaying the number of warning letters issued for all of FDA’s programs from fiscal year 2004 through 2011, including devices, drugs, food, biologics, veterinary medicine, and tobacco products. For example, out of 1,720 warning letters issued in 2011, 1,040 warning letters related to FDA’s regulation of tobacco products. As a result, the figure does not accurately reflect the number of actions FDA directed toward drug manufacturing. For example, we understand that, in fiscal year 2011, the Center for Drug Evaluation and Research (CDER) issued 108 warning letters. Please provide data to establish the number of warning letters issued by CDER for current good manufacturing practice (CGMP) violations from 2004 through 2011.**

As you mention, the 156 percent increase in FDA Warning Letters cited by the Committee’s report between 2010 and 2011 was unrelated to drug shortages; it was due primarily to the actions of the relatively new Center for Tobacco Products (CTP). The Agency was given authority over tobacco products by Congress in June 2009, and in 2010 and 2011 began

contracting with states to inspect retailers for compliance with the Federal Food, Drug, and Cosmetic Act (FD&C Act or the Act). CTP issued 1,040 Warning Letters in 2011, 60 percent of all Warning Letters issued that year.

As the graphic below demonstrates, from 2008 to 2011—the time period when there was a dramatic increase in drug shortages—the level of Warning Letters issued to firms for quality deficiencies in the manufacture of human drugs or biological products remained relatively flat.



The actual pattern of relevant Warning Letters issued by the Center for Biologics Evaluation and Research (CBER) and CDER shows modest fluctuation, following the quality problems the Agency identified at manufacturing facilities. The number of relevant Warning Letters issued between 2008 and 2011 were:

- 2008: 30 manufacturing deficiency Warning Letters (7 percent of all Warning Letters that FDA issued that year)
- 2009: 34 manufacturing deficiency Warning Letters (7 percent of all Warning Letters that FDA issued that year)
- 2010: 60 manufacturing deficiency Warning Letters (9 percent of all Warning Letters that FDA issued that year)
- 2011: 48 manufacturing deficiency Warning Letters (3 percent of all Warning Letters that FDA issued that year)

To summarize, the data clearly indicate that the number of Warning Letters relevant to drug products has not increased radically, as the report suggests. They are not the root cause of the recent increase in drug shortages.

5. The report suggests that drug shortages increased with the number of warning letters FDA issued. Please describe the timeline of events related to shortages with respect to FDA inspections, warning letters, shortages, and shutdowns. Please also indicate if FDA implemented a material shift in the practice of CGMP inspections over the past three years.

There have been no recent changes to the cGMP standards or inspection processes that would substantially impact compliance for product manufacturing, including manufacture of sterile injectables.

Above, we provided information about the timelines of events related to shortages and Warning Letters. As we said there, drug shortages began increasing years before the period highlighted in the Report, and there has not been a radical increase in relevant Warning Letters, as suggested in the Report. The common thread in Warning Letters is that, in each case, FDA has identified serious defects in safety procedures or in products that posed a risk to patients.

FDA inspections do not cause firms to have manufacturing or quality problems, which are the root cause of many shutdowns. In fact, FDA has often conducted inspections to follow up on reports from manufacturers, after the manufacturer has identified manufacturing or quality problems or has received reports from practitioners and patients regarding quality issues with a drug. How FDA and firms respond to inspection results depends on the facts of each particular case. Where serious problems are found, FDA may send a Warning Letter. In the cases discussed in our answers to Question 1, safety concerns led first to targeted efforts to protect patients and remediate problems. Where shutdowns occurred, they were in the context of serious, unresolved safety concerns and were not ordered by FDA.

FDA remains extremely concerned about the serious public health issues presented by the drug shortage crisis. We are committed to continuing to work with industry, health care professionals, patients, and other stakeholders to avert drug shortages and to help keep critical products on the market. At the same time, we must balance the risks to patients posed by product quality problems against the risks associated with a shortage to achieve our ultimate goal of ensuring patient access to medicines that are safe and effective.

Thank you, again, for contacting us concerning this matter. Please let us know if you have any further questions.

Sincerely,



Jeanne Ireland
Assistant Commissioner
for Legislation

Enclosure

cc: The Honorable Darrell E. Issa
Chairman
Committee on Oversight and Government Reform